

REMARKS

Claims 1-16 and 18-39 are pending in the present application. Claims 19 and 31 are amended. Support for the amendment can be found, for example, in the specification on page 16, lines 1-3. Applicants reserve the right to prosecute canceled subject matter in continuing applications. All claim amendments are made without prejudice and do not represent an acquiescence in any ground of rejection.

Rejection under 35 U.S.C § 112, First Paragraph, Enablement

Claims 19, 31, and 37-39 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement for methods of treating any type of cancer or Alzheimer's disease. Although Applicants do not agree, Applicants have amended claims 19 and 31 to specify that cancer to be treated with the present methods is either ovarian or breast cancer.

With respect to the assertion that there is no established correlation between the use of compounds that inhibit PAI-1 activity and Alzheimer's disease, Applicants herein submit a number of references describing the role of the plasminogen system in neural degeneration and Alzheimer's Disease. Also submitted are a number of references describing the role of the plasminogen system in various cancers, including ovarian and breast cancer.

Condition	Reference
Alzheimer's disease	Periz and Fortini, <i>EMBO Reports</i> , 1:477-478, 2000; Tucker et al. <i>J. Neurosci.</i> 20:3937-3946, 2000; Kingston et al. <i>Nat. Med.</i> 1:138-142, 1995; Wnendt et al. <i>Thromb. Res.</i> 8:217-224, 1997; Van Nostrand and Porter, <i>Biochemistry</i> 38:11570-11576, 1999; Exley and Korchazhkina, <i>Neuroreport.</i> 12:2967-2970, 2001; Tucker et al. <i>J. Neurochem.</i> 75:2172-2177, 2000; Tsirka et al. <i>J. Neurosci.</i> 17:543-552 1997; Seeds et al. <i>PNAS</i> , 96:14118-14123, 1999; McGeer and McGeer, <i>Brain Res. Rev.</i> 21:195-218, 1995; Rebeck et al. <i>Ann. Neurol.</i> 37:211-217, 1995 (to be supplied to Examiner upon receipt;

Condition	Reference
	Ledesma et al. <i>EMBO Reports</i> , 1:530-535, 2000; Simons et al. <i>PNAS</i> 95:6460-6464, 1998; Melchor et al. <i>J. Neurosci.</i> 23:8867-8871, 2003; Tucker et al. <i>J. Neurosci. Res.</i> 70:249-255, 2002; Kim et al. <i>Science</i> , 284:647-650, 1999; Fay et al. <i>Blood</i> 90:204-208, 1997; Carmeliet et al. <i>Ann. NY Acad Sci</i> , 748:367-381, 1995;
Cancer	
PAI-1 is potential new target for antiinvasive and antimetastatic therapy	Frandsen, Thomas Leth; Stephens, Ross W.; Pedersen, Anders Navrsted; Engelholm, Lars H.; Holst-Hansen, Claus; Brunner, Nils. <i>Drugs of the Future</i> (1998), 23(8), 873-883
PAI-1 promotes angiogenesis by stimulating endothelial cell migration toward fibronectin	Isogai, Chiho; Laug, Walter E.; Shimada, Hiroyuki; Declerck, Paul J.; Stins, Monique F.; Durden, Donald L.; Erdreich-Epstein, Anat; DeClerck, Yves A. <i>Cancer Research</i> (2001), 61(14), 5587-5594
Clinical significance of the expression of urokinase type plasminogen activator and plasminogen activator inhibitor in cervical carcinomas	Qu, Muwen; Sheng, Xiugui; Wei, Ling. <i>Zhongliu Fangzhi Zazhi</i> (2003), 10(8), 821-824
Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients	Look, Maxime P.; van Putten, Wim L. J.; Duffy, Michael J.; Harbeck, Nadia; Christensen, Ib Jarle; Thomssen, Christoph; Kates, Ronald; Spyratos, Frederique; Ferno, Marten; Eppenberger-Castori, Serenella; Sweep, C. G. J.; Ulm, Kurt; Peyrat, Jean-Philippe; Martin, Pierre-Marie; Magdelenat, Henri; Brunner, Nils; Duggan, Catherine; Lisboa, Bjorn W.; Bendahl, Par-Ola; Quillien, Veronique; Daver, Alain; Ricolleau, Gabriel; Meijer-van Gelder, Marion E.; Manders, Peggy; Fiets, W. Edward; Blankenstein, Marinus A.; Broet, Philippe; Romain, Sylvie; Daxenbichler, Gunter; Windbichler, Gudrun; Cufer, Tanja; Borstnar, Simona; Kueng, Willy; Beex, Louk V. A. M.; Klijn, Jan G. M.; O'Higgins, Niall; Eppenberger, Urs; Janicke, Fritz; Schmitt, Manfred; Foekens, John A. <i>Journal of the National Cancer Institute</i> (2002), 94(2), 116-128
Promigratory effect of plasminogen activator inhibitor-1 on invasive breast cancer cell populations	Chazaud, Benedicte; Ricoux, Remy; Christov, Christo; Plonquet, Anne; Gherardi, Romain K.; Barlovatz-Meimon, Georgia. <i>American Journal of Pathology</i> (2002), 160(1), 237-246

Condition	Reference
A regulatory hydrophobic area in the flexible joint region of plasminogen activator inhibitor-1, defined with fluorescent activity-neutralizing ligands. Ligand-induced serpin polymerization.	Egelund, Rikke; Einholm, Anja P.; Pedersen, Katrine E.; Nielsen, Rasmus W.; Christensen, Anni; Deinum, Johanna; Andreasen, Peter A. <i>Journal of Biological Chemistry</i> (2001), 276(16), 13077-13086
Epitope mapping for four monoclonal antibodies against human plasminogen activator inhibitor type- 1. Implications for antibody-mediated PAI-1 - neutralization and vitronectin-binding	Wind, Troels; Jensen, Mads A.; Andreasen, Peter A. <i>European Journal of Biochemistry</i> (2001), 268(4), 1095-1106
Endocrinological contribution of sex steroids for invasion and metastasis in uterine endometrial cancer and its clinical implication	Ichigo, Satoshi; Fujimoto, Jiro; Tamaya, Teruhiko. <i>Gifu Daigaku Igakubu Kiyo</i> (1997), 45(1), 133-146
Expression of type-1 plasminogen activator inhibitor in breast carcinoma tissues	Tang, Huibin; Zhou, Zhongweng; Zhang, Xiaohua; Sun, Dongfeng; Song, Houyan; Zhu, Yunsong. <i>Shanghai Yike Daxue Xuebao</i> (1996), 23(3), 189-193
Immunohistochemical localization of the plasminogen activator inhibitor-1 in breast cancer	Bianchi, Elisabetta; Cohen, Robert L.; Dai, Aihua; Thor, Ann T.; Shuman, Marc A.; Smith, Helene S. <i>International Journal of Cancer</i> (1995), 60(5), 597-603
Immunohistochemical expression of uPA, PAI-1 , cathepsin D and apoptotic cells in ductal carcinoma <i>in situ</i> of the breast	Zhao Haiying; Morimoto Tadaoki; Sasa Mitsunori; Tanaka Takashi; Izumi Keisuke <i>Breast cancer</i> (Tokyo, Japan) (2002), 9(2), 118-26
Association of urokinase-type plasminogen activator and its inhibitor with disease progression and prognosis in ovarian cancer	Konecny G; Untch M; Pihan A; Kimmig R; Gropp M; Stieber P; Hepp H; Slamon D; Pegram M <i>Clinical cancer research</i> (2001), 7(6), 1743-9
Primary Tumor and Metastasis in Ovarian Cancer Differ in Their Content of Urokinase-type Plasminogen Activator, Its Receptor, and Inhibitors Type 1 and 2	Schmalfeldt B; Kuhn W; Reuning U; Pache L; Dettmar P; Schmitt M; Janicke F; Hofler H; Graeff H; <i>Cancer Research</i> (1995), 55, 3958-3963
Plasminogen activator inhibitor-	Chambers S K; Ivins C M; Carcangiu M L

Condition	Reference
1 is an independent poor prognostic factor for survival in advanced stage epithelial ovarian cancer patients	<i>International journal of cancer</i> . (1998), 79(5), 449-54
Protease levels in breast, ovary, and other gynecological tumor tissues: prognostic importance in breast cancer	Ruppert C; Ehrenforth S; Scharrer I; Halberstadt E <i>Cancer detection and prevention</i> (1997), 21(5), 452-9 (abstract only)
pS2 and PAI - 1 in ovarian cancer : correlation to pathohistological parameters.	Speiser P; Mayerhofer K; Kucera E; Roch G; Mittelbock M; Gitsch G; Zeillinger R <i>Anticancer research</i> (1997), 17(1B), 679-83 (abstract only)

Because a skilled artisan could carry out the claimed methods, without undue experimentation; and because there is an established correlation between the use of compounds that inhibit PAI-1 activity and Alzheimer's disease and cancer, Applicants respectfully request that the rejection of claims 19 and 31 for alleged lack of enablement be withdrawn.

Claims 20-30 also appear to be rejected for alleged lack of enablement for methods of treating any type of cancer or Alzheimer's disease. Claims 20-30, however, are directed to diseases other than Alzheimer's disease and cancer. It is Applicant's understanding that the Action has acknowledged that methods of treating these diseases are enabled. Accordingly, Applicants respectfully request that the rejection of claims 19 and 31 for alleged lack of enablement be withdrawn.

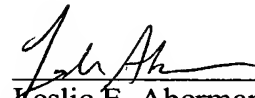
Applicants respectfully submit that the present application is in condition for allowance. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number

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provided. Favorable consideration and an early notice of allowance are respectfully requested.

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